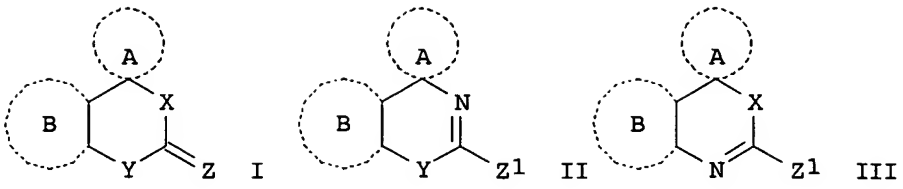
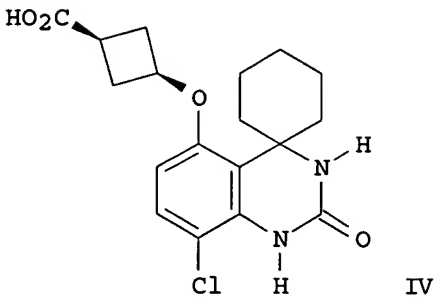
```
 * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 11:38:30 ON 13 MAR 2007

=> file caplus medline biosis embase
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.42       0.42

FILE 'CAPLUS' ENTERED AT 11:39:37 ON 13 MAR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 11:39:37 ON 13 MAR 2007

FILE 'BIOSIS' ENTERED AT 11:39:37 ON 13 MAR 2007
Copyright (c) 2007 The Thomson Corporation

FILE 'EMBASE' ENTERED AT 11:39:37 ON 13 MAR 2007
Copyright (c) 2007 Elsevier B.V. All rights reserved.

=> s allodyni?
L1        10423 ALLODYNI?

=> s naltrexone
L2        21983 NALTREXONE

=> s l1 and l2
L3           51 L1 AND L2

=> dup rem
ENTER L# LIST OR (END):l3
PROCESSING COMPLETED FOR L3
L4            33 DUP REM L3 (18 DUPLICATES REMOVED)
                 ANSWERS '1-13' FROM FILE CAPLUS
                 ANSWERS '14-21' FROM FILE MEDLINE
                 ANSWERS '22-23' FROM FILE BIOSIS
                 ANSWERS '24-33' FROM FILE EMBASE

=> d ti au abs so py 1-10 l3

L3   ANSWER 1 OF 51  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Preparation of spiro[cyclohexane-1,4'-quinazoline] derivatives for use as
     PDE7 inhibitors for the treatment of neuropathic pain
IN   Cox, Peter; Kinloch, Ross Anderson; Maw, Graham Nigel
GI
```




IV

AB Compds. I-III [Ring B = (un)substituted six-membered aryl or heteroaryl ring; Ring A = (un)substituted spirocycle or spiroheterocycle; X = O or NH, NNH2, etc.; Y = O, S, NH, etc.; Z = CHNO2, O, S, etc.; Z1 = H, Me, NH2, etc.] are disclosed as phosphodiesterase 7 (PDE7) inhibitors for use in the manufacture of a medicament for the treatment of neuropathic pain and to a method of treating neuropathic pain using an inhibitor of PDE7. Methods for preparing title compds. are given. Thus, e.g., IV was prepared by substitution of trans-3-[(benzyloxy)methyl]cyclobutyl p-toluenesulfonate (preparation given) with 8'-chloro-5'-hydroxy-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one followed by deprotection and oxidation In PDE7A inhibition assays, IV demonstrated a Ki value of 1.9 (nM).
SO PCT Int. Appl., 108pp.
CODEN: PIXXD2
PY 2006
2006

L3 ANSWER 2 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Remedy for neuropathic pain
IN Tanabe, Tsutomu
AB It is intended to provide a remedy for neuropathic pain capable of exhibiting an excellent therapeutic effect on neuropathic pain which is an intractable disease. More specifically speaking, a remedy for neuropathic pain which contains an opioid receptor antagonist (in particular, naloxone, naltrexone, naloxonazine, naltrindole, etc.) as the active ingredient; a medicinal composition for treating neuropathic pain which contains an opioid receptor antagonist as the active ingredient; a method of treating neuropathic pain by using an opioid receptor antagonist, and so on.
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PY 2006
2006

L3 ANSWER 3 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Method of treating neuropathic pain using a CRTH2 receptor antagonist
IN Corradini, Laura; Field, Mark John; Kinloch, Ross Anderson; Williams-Jones, Bryn Ivor

AB The invention discloses the use of a CRTH2 receptor antagonist in the manufacture of a medicament for the treatment of neuropathic pain and to a method of treating neuropathic pain using an antagonist of CRTH2 receptor.
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
PY 2005
2006
2005
2007

L3 ANSWER 4 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Methods and materials for the treatment of pain comprising opioid antagonists
IN Burns, Lindsay H.; Schoenhard, Grant L.
AB Methods and compns. for treating subjects with pain, including neuropathic pain, using opioid antagonists are described. Such antagonists are used alone or in combinations with opioid agonists, wherein an opioid antagonist enhances the neuropathic pain-alleviating potency of an opioid agonist. For example, the combination of naltrexone (0.1 ng) and morphine (10 μg), representing a ratio of 1:100,000 of the opioid antagonist to opioid agonist, twice daily, resulted in a significant antihyperalgesic effect in a rat model of neuropathic pain, compared to vehicle or morphine alone for the Day 1 through Day 7 duration. Although morphine alone at 10 μg resulted in 65% and 73% antihyperalgesia on Day 1 and 2, resp., with return to baseline by day 5, the combination of morphine (10 μg) and naltrexone (0.1 ng) resulted in 75, 81, 91, 63, 79, 67 and 56% antihyperalgesia on Days 1 through 7, resp., as well as analgesia (paw withdrawal latencies went above baseline) Days 1 through 7.
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
PY 2004
2005
2004
2004
2005
2006

L3 ANSWER 5 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Antiallodynic effects of loperamide and fentanyl against topical capsaicin-induced allodynia in unanesthetized primates
AU Butelman, Eduardo R.; Harris, Todd J.; Kreek, Mary Jeanne
AB Capsaicin produces thermal allodynia in animals and humans by acting as an agonist at vanilloid receptor subtype 1 [VR1; also known as transient receptor potential vanilloid type 1 (TRPV1)]. VR1 receptors are widely distributed in the periphery (e.g., on primary afferent neurons). These studies examined the ability of loperamide (0.1-1 mg/kg s.c.; a μ-opioid agonist that is peripherally selective after systemic administration), in preventing and reversing thermal allodynia caused by topical capsaicin (0.004 M) in rhesus monkeys, within a tail withdrawal assay (n = 4; 38 and 42; normally non-noxious thermal stimuli). The effects of loperamide were compared with those of the centrally penetrating μ-agonist, fentanyl (0.0032-0.032 mg/kg s.c.). We also characterized the allodynic effects of the endogenous VR1 agonist ("endovanilloid"), N-oleoyldopamine (OLDA; 0.0013-0.004 M). In this model, loperamide and fentanyl produced dose-dependent prevention of capsaicin-induced allodynia, whereas only fentanyl produced robust reversal of ongoing allodynia. Antagonism expts. with naltrexone (0.1 mg/kg s.c.) or its analog, methylnaltrexone (0.32 mg/kg s.c.), which does not readily cross the blood-brain barrier, suggest that the antiallodynic effects of loperamide and fentanyl were predominantly mediated by peripherally and centrally located μ-receptors, resp. Loperamide and fentanyl (1 mg/kg and 0.032 mg/kg, resp.) also prevented OLDA (0.004 M)-induced allodynia. Up to

the largest dose studied, loperamide was devoid of thermal antinociceptive effects at 48 (a noxious thermal stimulus, in the absence of capsaicin). By contrast, fentanyl (0.01-0.032 mg/kg) caused dose-dependent antinociception in this sensitive thermal antinociceptive assay (a presumed centrally mediated effect). These studies show that loperamide, acting as a peripherally selective μ-agonist after systemic administration, can prevent capsaicin-induced thermal allodynia in primates in vivo, in the absence of thermal antinociceptive effects.

SO Journal of Pharmacology and Experimental Therapeutics (2004), 311(1), 155-163
CODEN: JPETAB; ISSN: 0022-3565

PY 2004

L3 ANSWER 6 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Supraspinal anti-allodynic and rewarding effects of endomorphins in rats

AU Huang, Eagle Yi-Kung; Chen, Ching-Ming; Tao, Pao-Luh

AB Two potent endogenous opioid peptides, endomorphin-1 (EM-1) and -2 (EM-2), which are selective μ-opioid agonists, have been identified from bovine and human brain. These endomorphins were demonstrated to produce a potent anti-allodynic effect at spinal level. In the present study, the authors further investigated their supraspinal anti-allodynic effects and rewarding effects. In a neuropathic pain model (sciatic nerve crush in rats), EM-1 and -2 (15 μg, i.c.v.) both showed significant suppressive effects in the cold-water allodynia test, but EM-1 showed a longer duration than EM-2. Naltrexone (NTX; 15 μg) and naloxonazine (NLZ; 15 μg) were both able to completely block the anti-allodynic effects of EM-1 and -2. In the tests of conditioned place preference (CPP), only EM-2 at the dose of 30 μg showed significant pos. rewarding effect, whereas both endomorphins did not induce any reward at the dose of 15 μg. Due to the low solubility and the undesired effect (barrel rotation of the body trunk), EM-1 was not tested for the dose of 30 μg in the CPP tests. It was also found that acute EM-2 (30 μg) administration increased dopamine turnover in the shell of nucleus accumbens in the microdialysis expts. From these results, it may be suggested that EM-1 and -2 could be better supraspinal anti-allodynic agents compared with the other opioid drugs, although they may also induce rewarding.

SO Peptides (New York, NY, United States) (2004), 25(4), 577-583
CODEN: PPTDD5; ISSN: 0196-9781

PY 2004

L3 ANSWER 7 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Suppression of acute herpetic pain-related responses by the κ-opioid receptor agonist (-)-17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-3-trans-3-(3-furyl) acrylamido] morphinan hydrochloride (TRK-820) in mice

AU Takasaki, Ichiro; Suzuki, Tomohiko; Sasaki, Atsushi; Nakao, Kaoru; Hirakata, Mikito; Okano, Kiyoshi; Tanaka, Toshiaki; Nagase, Hiroshi; Shiraki, Kimiyasu; Nojima, Hiroshi; Kuraishi, Yasushi

AB (-)-17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-3-trans-3-(3-furyl) acrylamido] morphinan hydrochloride (TRK-820) is a κ-opioid receptor agonist that has pharmacol. characteristics different from typical κ-opioid receptor agonists. This study was conducted to determine the antiallodynic and antihyperalgesic effects of TRK-820 in a mouse model of acute herpetic pain and to compare them with those of the κ-opioid receptor agonist enadoline and the μ-opioid receptor agonist morphine. Percutaneous inoculation with herpes simplex virus type-1 induced tactile allodynia and mech. hyperalgesia in the hind paw on the inoculated side. TRK-820 (0.01 - 0.1 mg/kg p.o.), enadoline (1 - 10 mg/kg p.o.) and morphine (5 - 20 mg/kg p.o.) dose dependently inhibited the allodynia and hyperalgesia, but the antiallodynic and antihyperalgesic dose of enadoline markedly decreased spontaneous locomotor activity. The antinociceptive action of TRK-820

(0.1 mg/kg) was completely antagonized by pretreatment with norbinaltorphimine, a κ-opioid receptor antagonist, but not by naltrexone, a μ-opioid receptor antagonist. Repeated treatment with morphine (20 mg/kg, four times) resulted in the reduction of antiallodynic and antihyperalgesic effects, whereas the inhibitory potency of TRK-820 (0.1 mg/kg) was almost the same even after the fourth administration. There was no cross-tolerance in antinociceptive activities between TRK-820 and morphine. Intrathecal and intracerebroventricular, but not intraplantar, injections of TRK-820 (10-100 ng/site) suppressed the allodynia and hyperalgesia. These results suggest that TRK-820 inhibits acute herpetic pain through κ-opioid receptors in the spinal and supraspinal levels. TRK-820 may have clin. efficacy in acute herpetic pain with enough safety margins.

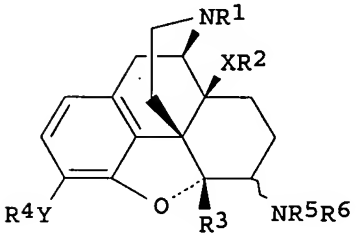
SO Journal of Pharmacology and Experimental Therapeutics (2004), 309(1), 36-41
CODEN: JPETAB; ISSN: 0022-3565
PY 2004

L3 ANSWER 8 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

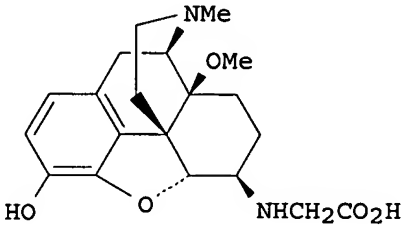
TI Method for the production of 6-aminomorphinan derivatives and their use as highly active analgesics

IN Schuetz, Johannes; Schmidhammer, Helmut

GI




I




II

AB The invention relates to the compds., e.g., I [R1 = H, C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C1-6-monohydroxyalkyl, C1-6-dihydroxyalkyl, C1-6-trihydroxyalkyl, C3-10-cycloalkyl-C1-6-alkyl, C3-10-cycloalkyl-C2-6-alkenyl, C3-10-cycloalkyl-C2-6-alkynyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C2-6-alkenyl, C6-10-aryl-C2-6-alkynyl; R2 = R1, C2-6-alkanoyl, C3-6-alkenoyl, C3-6-alkynoyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C3-6-alkenoyl, C6-10-aryl-C3-6-alkynoyl; R3 = H, C1-6-alkyl, C2-6-alkenyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C2-6-alkenyl, C1-6-alkoxy, -C1-6-alkyl, CO2(C1-6-alkyl), CO2H, CH2OH; R4 = C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C3-10-cycloalkyl-C1-6-alkyl, C3-10-cycloalkyl-C2-6-alkenyl, C3-10-cycloalkyl-C2-6-alkynyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C2-6-alkenyl, C6-10-aryl-C2-6-alkynyl, etc.; R5, R6 = H C3-10-cycloalkyl-C1-6-alkyl, C3-10-cycloalkyl-C2-6-alkenyl, C3-10-cycloalkyl-C2-6-alkynyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C2-6-alkenyl, C6-10-aryl-C2-6-alkynyl, etc.; X = O, S, CH2; XR2 = H; Y = O; YR4 = H], and their pharmaceutically acceptable acid addition salts, which are useful as highly active analgesics. Thus, aminomorphinan II·1.5 CF3CO2H was prepared from 14-O-methoxymorphone hydrobromide via reductive amination with glycine tert-Bu ester in MeOH containing NaCNBH3 followed by deesterification with CF3CO2H in CH2Cl2. Aminomorphinan II·1.5 CF3CO2H was tested for analgesic activity [Ki = 0.83 nM for opioid receptor; ED50 = 28 μg/kg s.c. and ED50 = 0.42 μg/kg i.cv. in rat tail flick test; ED50 = 500 μg/kg s.c. and ED50 = 0.42 μg/kg i.cv. respiratory depression in rats; ED50 = 100 μg/kg s.c. antiallodynic effect in rats].

SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
PY 2003
2003
2003
2003
2004
2006
2004
2005
2005
2005
2006
2006
2005
2006
2004
2005

L3 ANSWER 9 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Gabapentin antinociception in mice with acute herpetic pain induced by herpes simplex virus infection
AU Takasaki, Ichiro; Andoh, Tsugunobu; Nojima, Hiroshi; Shiraki, Kimiyasu; Kuraishi, Yasushi
AB The effects of systemic and local injections of gabapentin, a novel anticonvulsant agent, were tested on nociceptive behaviors in mice with acute herpetic pain. Transdermal infection with herpes simplex virus type-1 (HSV-1) produced nociceptive hypersensitivity of the infected hind paw to innocuous (allodynia) and noxious mech. stimulation (hyperalgesia) with von Frey filaments. Systemic administration of gabapentin (10-100 mg/kg, peroral) produced a dose-dependent inhibition of both allodynia and hyperalgesia; gabapentin (30-300 mg/kg) did not affect locomotor activity. Intrathecal injection of gabapentin (10-100 μg/animal) also attenuated dose dependently both nociceptive hypersensitivities. In contrast, intraplantar, intracisternal, and intracerebroventricular administration of gabapentin (10-100 μg/animal) had no effect on the HSV-1-induced nociceptive hypersensitivities. Pretreatment with naltrexone (1 mg/kg) inhibited antinociceptive effect of morphine (5 mg/kg), but not gabapentin (100 mg/kg). Repeated administration of morphine (5 mg/kg, four times) led to tolerance of antinociceptive action, whereas gabapentin (100 mg/kg, four times) had antinociceptive effect even after the fourth administration. The present results suggest that gabapentin is effective in the treatment of acute herpetic pain without apparent adverse effects, and analgesic action of gabapentin is mainly mediated by actions on the spinal cord.
SO Journal of Pharmacology and Experimental Therapeutics (2001), 296(2), 270-275
CODEN: JPETAB; ISSN: 0022-3565
PY 2001

L3 ANSWER 10 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI The role of peripheral Mu opioid receptors in the modulation of capsaicin-induced thermal nociception in rhesus monkeys
AU Ko, Mei-Chuan; Butelman, Eduardo R.; Woods, James H.
AB Capsaicin produces burning pain, followed by nociceptive responses, such as allodynia and hyperalgesia in humans and rodents. In the present study, when administered s.c. into the tail of rhesus monkeys, capsaicin (0.01-0.32 mg) dose-dependently produced thermal allodynia manifested as reduced tail-withdrawal latencies in 46°C water, from a maximum value of 20 s to approx. 2 s. Coadministration of selective mu opioid agonists, fentanyl (0.003-0.1 mg) and (D-Ala2,N-Me-Phe4, Gly5-ol)-enkephalin (0.001-0.03 mg), dose-dependently inhibited capsaicin-induced allodynia. This local antinociception was antagonized by small doses of opioid

antagonists, quadazocine (0.03 mg) and quaternary naltrexone (1 mg), applied locally in the tail. However, these doses of antagonists injected s.c. in the back did not antagonize local fentanyl. Comparing the relative potency of either agonist or antagonist after local and systemic administration confirmed that the site of action of locally applied mu opioid agonists is in the tail. These results provide evidence that activation of peripheral mu opioid receptors can diminish capsaicin-induced allodynia in primates. This exptl. pain model could be a useful tool for evaluating peripherally acting antinociceptive agents without central side effects and enhance new approaches to the treatment of inflammatory pain.

SO Journal of Pharmacology and Experimental Therapeutics (1998), 286(1), 150-156
CODEN: JPETAB; ISSN: 0022-3565

PY 1998

=> d ti au abs so py 11-20 l3

L3 ANSWER 11 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN

TI Effects of Korean red ginseng extract on neuropathic pain induced by chronically constrictive ligatures of the sciatic nerve in the rat

AU Kim, Young-In; Kim, Kwang-Jin

AB Mech. injuries of peripheral nerves disturb the reciprocal fast and slow communication between periphery and central nervous system and may lead to variety of clin. pain syndromes, including the hyperalgesia, allodynia, and spontaneous pain. One of the effective animal models used for this study is the "chronic constriction injury (CCI)" method, described by Bennett and Xie. The extract of Korean red ginseng (Panax ginseng C.A. Meyer) has been known to produce a variety of effects mediated by central nervous system. Especially, it showed inhibitory effect on morphine tolerance and dependence, and decreased the serotonin release from the brain stem. Recent studies suggested that the extract clearly showed analgesic and hypothermic effects in the rat at relatively high doses, and these effects were not mediated via endogenous opiates or opiate receptors since the effects were not antagonized by naltrexone. This study was undertaken to determine the effects and their mechanisms of a standard Korean red ginseng extract on peripheral neuropathic pain induced by the CCI method. The hind paw withdrawal responses as a indicator of pain were determined by the mech. (von Frei filaments: 0.8 gm and 4.2 gm), thermal (5°C, 30°C and 44°C) and acetone stimuli to compare with both effects before and after the i.p. injection of ginseng extract (200 mg/kg). Morphine (5 mg/kg, i.m.), ketamine (3 mg/kg, i.m.), and guanethidine (30 mg/kg, i.p.) were administered after injection of ginseng extract The results of the present study were summarized as follows:. 1. Ginseng extract did not show a significant analgesic effect in mech. allodynia and thermal hyperalgesia and allodynia. 2. Ginseng extract increased the hind paw sensitivity to some stimuli. 3. Ginseng extract produced significant inhibitory effect on the hind paw withdrawal responses to acetone stimuli. 4. Morphine showed inhibitory effect on the responses to noxious cold, acetone, and heat stimuli. The effects of morphine, however, were antagonized significantly by the ginseng extract 5. Ketamine, non-competitive antagonist of N-methyl-D-aspartate, showed significant inhibitory effect to noxious cold and acetone stimuli. 6. Guanethidine, chemical sympathetic blocker, showed no significant effects on the responses to noxious cold and heat stimuli, and acetone stimuli. These results suggested that the ginseng extract showed partially analgesic effect in disorders of pain sensation, and the hyperesthesia produced in this animal pain model was not dependent on the chemical sympathectomy. This effect might be a result from the depression of both the dorsal horn neurons in the spinal cord and the nociceptors sensitized by continuous impulse discharges at the nerve injury sites, and may be produced via a non-opioid mechanism.

SO Chungnam Uidae Chapchi (1995), 22(2), 209-223
CODEN: CUCHDS; ISSN: 0253-6307
PY 1995

L3 ANSWER 12 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Beneficial effect of the opioid receptor antagonist naltrexone on hypersensitivity induced by spinal cord ischemia in rats: disassociation with MK-801
AU Hao, J. X.; Xu, X. J.; Aldskogius, H.; Seiger, A.; Wiesenfeld-Hallin, Z.
AB In this study, the authors examined the effect of the long-acting opioid antagonist naltrexone on the allodynia-like effect of spinal ischemia in rats. The spinal cord ischemia was induced at midthoracic level by a recently developed photochem. technique using laser irradiation and photoactivatable intravascular dyes. An allodynia -like sensory disturbance, where the animals reacted by vocalization to non-noxious mech. stimuli in the flank area, was consistently seen during several days after ischemia. Pretreatment with 10 and 20 mg/kg, but not 5 mg/kg naltrexone i.v. 10 min before irradiation decreased the incidence of allodynia. However, even the effect of the highest dose of naltrexone (20 mg/kg) was incomplete, which is in contrast to the effect of the NMDA receptor antagonist MK-801, which has been tested in the same model and found to completely prevent the incidence of allodynia at a dose of 0.5 mg/kg. Pretreatment with sub- or suprathreshold doses of naltrexone (5 and 20 mg/kg resp.) combined with a subthreshold dose of MK-801 (0.1 mg/kg) did not produce a synergistic effect. When naltrexone (20 mg/kg) was administered 10 min after induction of ischemia, it was totally ineffective in decreasing the occurrence and severity of allodynia . In contrast, MK-801 (0.5 mg/kg) still had a good protective effect when injected at this time. Histol. examination showed slight morphol. damage in the spinal cord in 38% of control rats after 1 min laser irradiation without pretreatment with naltrexone. No morphol. abnormalities were observed in rats after pretreatment with naltrexone (20 mg/kg). The results suggest that opioid receptor antagonists and NMDA receptor antagonists prevent a consequence of transient spinal cord ischemia through different mechanisms. High doses of opioid antagonists may have anti-ischemic effects by improving local spinal cord microcirculation and therefore may have a role in preventing ischemia after traumatic spinal cord injury. On the other hand, the NMDA receptor may have a role in the secondary neuronal death resulting from ischemia. Thus, NMDA receptor antagonists may contribute to the prevention of tissue damage by antagonizing the excitotoxic action of glutamate and/or aspartate released by ischemia into the spinal cord. Finally, since only high doses of naltrexone had an effect in the present study, the authors cannot rule out the possibility that this drug may act through non-opioid mechanisms.
SO Restorative Neurology and Neuroscience (1991), 3(5), 257-66
CODEN: RNNEEL; ISSN: 0922-6028
PY 1991

L3 ANSWER 13 OF 51 CAPLUS COPYRIGHT 2007 ACS on STN
TI Pharmacology of the allodynia in rats evoked by high dose intrathecal morphine
AU Yaksh, T. L.; Harty, G. J.
AB Morphine sulfate in doses of 90 to 150 μg/3 μL evokes a prominent behavioral syndrome characterized by 1) periodic bouts of spontaneous agitation during which the rat scratches and bites at the skin of the caudal dermatomes and 2) vigorous agitation, vocalization and coordinated efforts to bite and escape evoked by a light tactile stimulus applied to the flank, suggestive of a pain state (allodynia). The phenomenon is not reversed by naltexone or is it subject to tolerance. The activities of related opioids and metabolites are discussed. Brief structure-activity relations are given. The observations that the sulfated and conjugated metabolites are 10 to 50 times more potent than

their unmetabolized precursor suggest the possibility that, in high concns., certain phenantherene opioid alkaloids with a free 3-OH position, an ether bridge and no N-Me extention will be subject to conjugation and this metabolite will alter the processing of otherwise innocuous tactile stimuli. The coding of light tactile stimulation as non-noxious requires a tonic modulatory influence at the spinal cord level. The fact that morphine at high concns. may exert anti-GABAergic and antiglycinergic effects and the ability of certain spinally administered inhibitory amino acid antagonists to mimic this effect supports this hypothesis.

SO Journal of Pharmacology and Experimental Therapeutics (1988), 244(2), 501-7
CODEN: JPETAB; ISSN: 0022-3565

PY 1988

L3 ANSWER 14 OF 51 MEDLINE on STN

TI Antiallodynic effects of loperamide and fentanyl against topical capsaicin-induced allodynia in unanesthetized primates.

AU Butelman Eduardo R; Harris Todd J; Kreek Mary Jeanne

AB Capsaicin produces thermal allodynia in animals and humans by acting as an agonist at vanilloid receptor subtype 1 [VR1; also known as transient receptor potential vanilloid type 1 (TRPV1)]. VR1 receptors are widely distributed in the periphery (e.g., on primary afferent neurons). These studies examined the ability of loperamide (0.1-1 mg/kg s.c.; a micro-opioid agonist that is peripherally selective after systemic administration), in preventing and reversing thermal allodynia caused by topical capsaicin (0.004 M) in rhesus monkeys, within a tail withdrawal assay (n = 4; 38 degrees C and 42 degrees C; normally non-noxious thermal stimuli). The effects of loperamide were compared with those of the centrally penetrating micro-agonist, fentanyl (0.0032-0.032 mg/kg s.c.). We also characterized the allodynic effects of the endogenous VR1 agonist ("endovanilloid"), N-oleoyldopamine (OLDA; 0.0013-0.004 M). In this model, loperamide and fentanyl produced dose-dependent prevention of capsaicin-induced allodynia, whereas only fentanyl produced robust reversal of ongoing allodynia. Antagonism experiments with naltrexone (0.1 mg/kg s.c.) or its analog, methylnaltrexone (0.32 mg/kg s.c.), which does not readily cross the blood-brain barrier, suggest that the antiallodynic effects of loperamide and fentanyl were predominantly mediated by peripherally and centrally located micro-receptors, respectively. Loperamide and fentanyl (1 mg/kg and 0.032 mg/kg, respectively) also prevented OLDA (0.004 M)-induced allodynia. Up to the largest dose studied, loperamide was devoid of thermal antinociceptive effects at 48 degrees C (a noxious thermal stimulus, in the absence of capsaicin). By contrast, fentanyl (0.01-0.032 mg/kg) caused dose-dependent antinociception in this sensitive thermal antinociceptive assay (a presumed centrally mediated effect). These studies show that loperamide, acting as a peripherally selective micro-agonist after systemic administration, can prevent capsaicin-induced thermal allodynia in primates in vivo, in the absence of thermal antinociceptive effects.

SO The Journal of pharmacology and experimental therapeutics, (2004 Oct) Vol. 311, No. 1, pp. 155-63. Electronic Publication: 2004-05-19.
Journal code: 0376362. ISSN: 0022-3565.

PY 2004

L3 ANSWER 15 OF 51 MEDLINE on STN

TI Supraspinal anti-allodynic and rewarding effects of endomorphins in rats.

AU Huang Eagle Yi-Kung; Chen Ching-Ming; Tao Pao-Luh

AB Two potent endogenous opioid peptides, endomorphin-1 (EM-1) and -2 (EM-2), which are selective micro-opioid agonists, have been identified from bovine and human brain. These endomorphins were demonstrated to produce a potent anti-allodynic effect at spinal level. In the present study, we further investigated their supraspinal anti-allodynic effects and rewarding effects. In a neuropathic pain model (sciatic nerve

crush in rats), EM-1 and -2 (15 microg, i.c.v.) both showed significant suppressive effects in the cold-water allodynia test, but EM-1 showed a longer duration than EM-2. Naltrexone (NTX; 15 microg) and naloxonazine (NLZ; 15 microg) were both able to completely block the anti-allodynic effects of EM-1 and -2. In the tests of conditioned place preference (CPP), only EM-2 at the dose of 30 microg showed significant positive rewarding effect, whereas both endomorphins did not induce any reward at the dose of 15 microg. Due to the low solubility and the undesired effect (barrel rotation of the body trunk), EM-1 was not tested for the dose of 30 microg in the CPP tests. It was also found that acute EM-2 (30 microg) administration increased dopamine turnover in the shell of nucleus accumbens in the microdialysis experiments. From these results, it may suggest that EM-1 and -2 could be better supraspinal anti-allodynic agents compared with the other opioid drugs, although they may also induce rewarding.
Copyright 2004 Elsevier Inc.
SO Peptides, (2004 Apr) Vol. 25, No. 4, pp. 577-83.
Journal code: 8008690. ISSN: 0196-9781.
PY 2004

L3 ANSWER 16 OF 51 MEDLINE on STN
TI Suppression of acute herpetic pain-related responses by the kappa-opioid receptor agonist (-)-17-cyclopropylmethyl-3,14beta-dihydroxy-4,5alpha-epoxy-beta-[n-methyl-3-trans-3-(3-furyl) acrylamido] morphinan hydrochloride (TRK-820) in mice.
AU Takasaki Ichiro; Suzuki Tomohiko; Sasaki Atsushi; Nakao Kaoru; Hirakata Mikito; Okano Kiyoshi; Tanaka Toshiaki; Nagase Hiroshi; Shiraki Kimiyasu; Nojima Hiroshi; Kuraishi Yasushi
AB (-)-17-Cyclopropylmethyl-3,14beta-dihydroxy-4,5alpha-epoxy-6beta-[N-methyl-3-trans-3-(3-furyl) acrylamido] morphinan hydrochloride (TRK-820) is a kappa-opioid receptor agonist that has pharmacological characteristics different from typical kappa-opioid receptor agonists. This study was conducted to determine the antiallodynic and antihyperalgesic effects of TRK-820 in a mouse model of acute herpetic pain and to compare them with those of the kappa-opioid receptor agonist enadoline and the mu-opioid receptor agonist morphine. Percutaneous inoculation with herpes simplex virus type-1 induced tactile allodynia and mechanical hyperalgesia in the hind paw on the inoculated side. TRK-820 (0.01-0.1 mg/kg p.o.), enadoline (1-10 mg/kg p.o.) and morphine (5-20 mg/kg p.o.) dose dependently inhibited the allodynia and hyperalgesia, but the antiallodynic and antihyperalgesic dose of enadoline markedly decreased spontaneous locomotor activity. The antinociceptive action of TRK-820 (0.1 mg/kg) was completely antagonized by pretreatment with norbinaltorphimine, a kappa-opioid receptor antagonist, but not by naltrexone, a mu-opioid receptor antagonist. Repeated treatment with morphine (20 mg/kg, four times) resulted in the reduction of antiallodynic and antihyperalgesic effects, whereas the inhibitory potency of TRK-820 (0.1 mg/kg) was almost the same even after the fourth administration. There was no cross-tolerance in antinociceptive activities between TRK-820 and morphine. Intrathecal and intracerebroventricular, but not intraplantar, injections of TRK-820 (10-100 ng/site) suppressed the allodynia and hyperalgesia. These results suggest that TRK-820 inhibits acute herpetic pain through kappa-opioid receptors in the spinal and supraspinal levels. TRK-820 may have clinical efficacy in acute herpetic pain with enough safety margins.
SO The Journal of pharmacology and experimental therapeutics, (2004 Apr) Vol. 309, No. 1, pp. 36-41. Electronic Publication: 2004-01-07.
Journal code: 0376362. ISSN: 0022-3565.
PY 2004

L3 ANSWER 17 OF 51 MEDLINE on STN
TI Reversal of ongoing thermal hyperalgesia in mice by a recombinant herpesvirus that encodes human preproenkephalin.
AU Yeomans David C; Jones Toni; Laurito Charles E; Lu Ying; Wilson Steven P

AB Herpesvirus-mediated transfer of the human preproenkephalin gene to primary afferent nociceptors prevents phasic thermal allodynia /hyperalgesia in mice. It is not known, however, whether similar viral treatments would reverse ongoing or chronic pain and allodynia /hyperalgesia. To this end, mice were given intrathecal injections of pertussis toxin (PTX), which produces a weeks-long thermal hyperalgesia apparently by uncoupling certain G proteins from inhibitory neurotransmitter receptors. This treatment produced profound thermal hyperalgesia in both Adelta and C-fiber thermonociceptive tests lasting at least 6 weeks. However, treatment of skin surfaces with an enkephalin-encoding herpesvirus, but not control virus or vehicle, completely reversed this hyperalgesia. This profound anti-hyperalgesia was observed for both Adelta- and C-fiber-mediated responses. Interestingly, however, while the anti-hyperalgesic effect of the enkephalin-encoding virus on C-fiber-mediated responses was reversed by intrathecal application of micro or delta opioid antagonists, only delta antagonists reversed the effect of this virus on Adelta hyperalgesia. Thus, virus-mediated delivery of the proenkephalin cDNA reverses thermal hyperalgesia produced by PTX-induced ribosylation of inhibitory G proteins by an opioid-mediated mechanism. These results suggest that herpesvirus vectors encoding analgesic peptides may be useful in attenuating centrally mediated, ongoing neuropathic pain and/or hyperalgesia.

SO Molecular therapy : the journal of the American Society of Gene Therapy, (2004 Jan) Vol. 9, No. 1, pp. 24-9.
Journal code: 100890581. ISSN: 1525-0016.
PY 2004

L3 ANSWER 18 OF 51 MEDLINE on STN

TI Enhancement of the effects of a complete inhibitor of enkephalin-catabolizing enzymes, RB 101, by a cholecystokinin-B receptor antagonist in diabetic rats.

AU Coudore-Civiale M A; Meen M; Fournie-Zaluski M C; Boucher M; Roques B P; Eschalier A

AB 1. RB 101, a complete inhibitor of enkephalin-catabolizing enzymes, has been previously shown to produce antinociception in normal rats after systemic administration. Moreover, its coadministration with a cholecystokinin-B (CCK-B) receptor antagonist has been shown to strongly enhance its antinociceptive effect in normal rats. In this work, we determined whether RB 101 was able to reduce hyperalgesia and allodynia in diabetic rats, a model of neuropathic pain. The type of opioid receptors (mu or delta) involved was determined using naloxone and naltrindole, respectively, and the interactions between endogenous enkephalins and CCK on nociception control was investigated using coadministration of RB 101 and the CCK-B receptor antagonist CI-988. 2. RB 101 suppressed mechanical hyperalgesia (paw pressure-induced vocalization test), partially alleviated mechanical allodynia (von Frey hair test), and was ineffective in thermal allodynia (tail immersion test). The analgesic effect was completely cancelled by naloxone or naltrindole, suggesting that is requires the availability of mu- and/or delta-opioid receptors. 3. The combination of an inactive dose of CI-988 with the lowest effective dose of RB 101 resulted in a stronger increase in the vocalization threshold comparatively to RB 101 alone. 4. The present study demonstrates that the antinociception generated by RB 101 induced by elevation of extracellular levels of endogenous enkephalins, can be extended to neuropathic pain in diabetic rats and that blockade of CCK-B receptors potentiated antinociceptive effects elicited by RB 101.

SO British journal of pharmacology, (2001 May) Vol. 133, No. 1, pp. 179-85.
Journal code: 7502536. ISSN: 0007-1188.
PY 2001

L3 ANSWER 19 OF 51 MEDLINE on STN

TI The role of delta-opioid receptor subtypes in neuropathic pain.

AU Mika J; Przewlocki R; Przewlocka B

AB A large body of evidence suggests an important role of delta-opioid receptor agonists in antinociception at the level of the spinal cord. Our study was undertaken to analyse the spinal antinociceptive and antiallodynic effects of delta(1)- and delta(2)-opioid receptor agonists and antagonist after their acute and chronic intrathecal administration in a neuropathic pain model in the rat. In rats with a crushed sciatic nerve, the delta(1)-opioid receptor agonist [D-Pen(2), D-Pen(5)]enkephalin (DPDPE, 5-25 microg i.t.) and the delta(2)-opioid receptor agonist deltorphin II (1.5-25 microg i.t.) dose dependently antagonized the cold-water allodynia which developed after sciatic nerve injury. These effects of DPDPE were antagonized by 7-benzylidenenaltrexon (BNTX, 1 microg i.t.) while the effects of deltorphin II were antagonized by 5'naltrindole izotiocyanate (5'NTII, 25 microg i.t.). Both agonists had a dose-dependent, statistically significant effect on the tail-flick latency in two tests, with focused light and cold water. Chronic administration of DPDPE (25 microg i.t.) and deltorphin II (15 microg i.t.) resulted in significant prolongation of the reaction time determined on days 2, 4 and 6 post-injury. In conclusion, our results show an antiallodynic and antinociceptive action of DPDPE and deltorphin II at the spinal cord level, which suggests that both delta-opioid receptor subtypes play a similar role in neuropathic pain. This indicates that not only delta(1)- but also delta(2)-opioid receptor agonists can be regarded as potential drugs for the therapy of neuropathic pain.

SO European journal of pharmacology, (2001 Mar 9) Vol. 415, No. 1, pp. 31-7.
Journal code: 1254354. ISSN: 0014-2999.
PY 2001

L3 ANSWER 20 OF 51 MEDLINE on STN

TI Gabapentin antinociception in mice with acute herpetic pain induced by herpes simplex virus infection.

AU Takasaki I; Andoh T; Nojima H; Shiraki K; Kuraishi Y

AB The effects of systemic and local injections of gabapentin, a novel anticonvulsant agent, were tested on nociceptive behaviors in mice with acute herpetic pain. Transdermal infection with herpes simplex virus type-1 (HSV-1) produced nociceptive hypersensitivity of the infected hind paw to innocuous (allodynia) and noxious mechanical stimulation (hyperalgesia) with von Frey filaments. Systemic administration of gabapentin (10-100 mg/kg, peroral) produced a dose-dependent inhibition of both allodynia and hyperalgesia; gabapentin (30-300 mg/kg) did not affect locomotor activity. Intrathecal injection of gabapentin (10-100 microg/animal) also attenuated dose dependently both nociceptive hypersensitivities. In contrast, intraplantar, intracisternal, and intracerebroventricular administration of gabapentin (10-100 microg/animal) had no effect on the HSV-1-induced nociceptive hypersensitivities. Pretreatment with naltrexone (1 mg/kg) inhibited antinociceptive effect of morphine (5 mg/kg), but not gabapentin (100 mg/kg). Repeated administration of morphine (5 mg/kg, four times) led to tolerance of antinociceptive action, whereas gabapentin (100 mg/kg, four times) had antinociceptive effect even after the forth administration. The present results suggest that gabapentin is effective in the treatment of acute herpetic pain without apparent adverse effects, and analgesic action of gabapentin is mainly mediated by actions on the spinal cord.

SO The Journal of pharmacology and experimental therapeutics, (2001 Feb) Vol. 296, No. 2, pp. 270-5.
Journal code: 0376362. ISSN: 0022-3565.
PY 2001

=>

```
=> d his

     (FILE 'HOME' ENTERED AT 11:38:30 ON 13 MAR 2007)

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 11:39:37 ON 13 MAR 2007
L1         10423 S ALLODYNI?
L2         21983 S NALTREXONE
L3            51 S L1 AND L2
L4            33 DUP REM L3 (18 DUPLICATES REMOVED)

=> d ti au abs so py 1-10 l4

L4   ANSWER 1 OF 33  CAPLUS  COPYRIGHT 2007 ACS on STN DUPLICATE 1
TI   Supraspinal anti-allodynic and rewarding effects of endomorphins
     in rats
AU   Huang, Eagle Yi-Kung; Chen, Ching-Ming; Tao, Pao-Luh
AB   Two potent endogenous opioid peptides, endomorphin-1 (EM-1) and -2 (EM-2),
     which are selective μ-opioid agonists, have been identified from bovine
     and human brain.  These endomorphins were demonstrated to produce a potent
     anti-allodynic effect at spinal level.  In the present study,
     the authors further investigated their supraspinal anti-allodynic
     effects and rewarding effects.  In a neuropathic pain model (sciatic nerve
     crush in rats), EM-1 and -2 (15 μg, i.c.v.) both showed significant
     suppressive effects in the cold-water allodynia test, but EM-1
     showed a longer duration than EM-2.  Naltrexone (NTX; 15 μg)
     and naloxonazine (NLZ; 15 μg) were both able to completely block the
     anti-allodynic effects of EM-1 and -2.  In the tests of
     conditioned place preference (CPP), only EM-2 at the dose of 30 μg
     showed significant pos. rewarding effect, whereas both endomorphins did
     not induce any reward at the dose of 15 μg.  Due to the low solubility and
     the undesired effect (barrel rotation of the body trunk), EM-1 was not
     tested for the dose of 30 μg in the CPP tests.  It was also found that
     acute EM-2 (30 μg) administration increased dopamine turnover in the
     shell of nucleus accumbens in the microdialysis expts.  From these
     results, it may be suggested that EM-1 and -2 could be better supraspinal
     anti-allodynic agents compared with the other opioid drugs,
     although they may also induce rewarding.
SO   Peptides (New York, NY, United States) (2004), 25(4), 577-583
     CODEN: PPTDD5; ISSN: 0196-9781
PY   2004

L4   ANSWER 2 OF 33  CAPLUS  COPYRIGHT 2007 ACS on STN DUPLICATE 2
TI   Antiallodynic effects of loperamide and fentanyl against topical
     capsaicin-induced allodynia in unanesthetized primates
AU   Butelman, Eduardo R.; Harris, Todd J.; Kreek, Mary Jeanne
AB   Capsaicin produces thermal allodynia in animals and humans by
     acting as an agonist at vanilloid receptor subtype 1 [VR1; also known as
     transient receptor potential vanilloid type 1 (TRPV1)].  VR1 receptors are
     widely distributed in the periphery (e.g., on primary afferent neurons).
     These studies examined the ability of loperamide (0.1-1 mg/kg s.c.; a
     μ-opioid agonist that is peripherally selective after systemic
     administration), in preventing and reversing thermal allodynia
     caused by topical capsaicin (0.004 M) in rhesus monkeys, within a tail
     withdrawal assay (n = 4; 38 and 42; normally non-noxious thermal stimuli).
     The effects of loperamide were compared with those of the centrally
     penetrating μ-agonist, fentanyl (0.0032-0.032 mg/kg s.c.).  We also
     characterized the allodynic effects of the endogenous VR1
     agonist ("endovanilloid"), N-oleoyldopamine (OLDA; 0.0013-0.004 M).  In
     this model, loperamide and fentanyl produced dose-dependent prevention of
     capsaicin-induced allodynia, whereas only fentanyl produced
     robust reversal of ongoing allodynia.  Antagonism expts. with
     naltrexone (0.1 mg/kg s.c.) or its analog, methylnaltrexone (0.32
     mg/kg s.c.), which does not readily cross the blood-brain barrier, suggest
```

that the antiallodynic effects of loperamide and fentanyl were predominantly mediated by peripherally and centrally located μ-receptors, resp. Loperamide and fentanyl (1 mg/kg and 0.032 mg/kg, resp.) also prevented OLDA (0.004 M)-induced allodynia. Up to the largest dose studied, loperamide was devoid of thermal antinociceptive effects at 48 (a noxious thermal stimulus, in the absence of capsaicin). By contrast, fentanyl (0.01-0.032 mg/kg) caused dose-dependent antinociception in this sensitive thermal antinociceptive assay (a presumed centrally mediated effect). These studies show that loperamide, acting as a peripherally selective μ-agonist after systemic administration, can prevent capsaicin-induced thermal allodynia in primates in vivo, in the absence of thermal antinociceptive effects.

SO Journal of Pharmacology and Experimental Therapeutics (2004), 311(1), 155-163
CODEN: JPETAB; ISSN: 0022-3565

PY 2004

L4 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3

TI Suppression of acute herpetic pain-related responses by the κ-opioid receptor agonist (-)-17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-3-trans-3-(3-furyl) acrylamido] morphinan hydrochloride (TRK-820) in mice

AU Takasaki, Ichiro; Suzuki, Tomohiko; Sasaki, Atsushi; Nakao, Kaoru; Hirakata, Mikito; Okano, Kiyoshi; Tanaka, Toshiaki; Nagase, Hiroshi; Shiraki, Kimiyasu; Nojima, Hiroshi; Kuraishi, Yasushi

AB (-)-17-Cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[N-methyl-3-trans-3-(3-furyl) acrylamido] morphinan hydrochloride (TRK-820) is a κ-opioid receptor agonist that has pharmacol. characteristics different from typical κ-opioid receptor agonists. This study was conducted to determine the antiallodynic and antihyperalgesic effects of TRK-820 in a mouse model of acute herpetic pain and to compare them with those of the κ-opioid receptor agonist enadoline and the μ-opioid receptor agonist morphine. Percutaneous inoculation with herpes simplex virus type-1 induced tactile allodynia and mech. hyperalgesia in the hind paw on the inoculated side. TRK-820 (0.01 - 0.1 mg/kg p.o.), enadoline (1 - 10 mg/kg p.o.) and morphine (5 - 20 mg/kg p.o.) dose dependently inhibited the allodynia and hyperalgesia, but the antiallodynic and antihyperalgesic dose of enadoline markedly decreased spontaneous locomotor activity. The antinociceptive action of TRK-820 (0.1 mg/kg) was completely antagonized by pretreatment with norbinaltorphimine, a κ-opioid receptor antagonist, but not by naltrexone, a μ-opioid receptor antagonist. Repeated treatment with morphine (20 mg/kg, four times) resulted in the reduction of antiallodynic and antihyperalgesic effects, whereas the inhibitory potency of TRK-820 (0.1 mg/kg) was almost the same even after the fourth administration. There was no cross-tolerance in antinociceptive activities between TRK-820 and morphine. Intrathecal and intracerebroventricular, but not intraplantar, injections of TRK-820 (10-100 ng/site) suppressed the allodynia and hyperalgesia. These results suggest that TRK-820 inhibits acute herpetic pain through κ-opioid receptors in the spinal and supraspinal levels. TRK-820 may have clin. efficacy in acute herpetic pain with enough safety margins.

SO Journal of Pharmacology and Experimental Therapeutics (2004), 309(1), 36-41
CODEN: JPETAB; ISSN: 0022-3565

PY 2004

L4 ANSWER 4 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4

TI Gabapentin antinociception in mice with acute herpetic pain induced by herpes simplex virus infection

AU Takasaki, Ichiro; Andoh, Tsugunobu; Nojima, Hiroshi; Shiraki, Kimiyasu; Kuraishi, Yasushi

AB The effects of systemic and local injections of gabapentin, a novel anticonvulsant agent, were tested on nociceptive behaviors in mice with

acute herpetic pain. Transdermal infection with herpes simplex virus type-1 (HSV-1) produced nociceptive hypersensitivity of the infected hind paw to innocuous (allodynia) and noxious mech. stimulation (hyperalgesia) with von Frey filaments. Systemic administration of gabapentin (10-100 mg/kg, peroral) produced a dose-dependent inhibition of both allodynia and hyperalgesia; gabapentin (30-300 mg/kg) did not affect locomotor activity. Intrathecal injection of gabapentin (10-100 μg/animal) also attenuated dose dependently both nociceptive hypersensitivities. In contrast, intraplantar, intracisternal, and intracerebroventricular administration of gabapentin (10-100 μg/animal) had no effect on the HSV-1-induced nociceptive hypersensitivities. Pretreatment with naltrexone (1 mg/kg) inhibited antinociceptive effect of morphine (5 mg/kg), but not gabapentin (100 mg/kg). Repeated administration of morphine (5 mg/kg, four times) led to tolerance of antinociceptive action, whereas gabapentin (100 mg/kg, four times) had antinociceptive effect even after the fourth administration. The present results suggest that gabapentin is effective in the treatment of acute herpetic pain without apparent adverse effects, and analgesic action of gabapentin is mainly mediated by actions on the spinal cord.

SO Journal of Pharmacology and Experimental Therapeutics (2001), 296(2), 270-275
CODEN: JPETAB; ISSN: 0022-3565
PY 2001

L4 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5

TI The role of peripheral Mu opioid receptors in the modulation of capsaicin-induced thermal nociception in rhesus monkeys

AU Ko, Mei-Chuan; Butelman, Eduardo R.; Woods, James H.

AB Capsaicin produces burning pain, followed by nociceptive responses, such as allodynia and hyperalgesia in humans and rodents. In the present study, when administered s.c. into the tail of rhesus monkeys, capsaicin (0.01-0.32 mg) dose-dependently produced thermal allodynia manifested as reduced tail-withdrawal latencies in 46°C water, from a maximum value of 20 s to approx. 2 s. Coadministration of selective mu opioid agonists, fentanyl (0.003-0.1 mg) and (D-Ala2,N-Me-Phe4, Gly5-ol)-enkephalin (0.001-0.03 mg), dose-dependently inhibited capsaicin-induced allodynia. This local antinociception was antagonized by small doses of opioid antagonists, quadazocine (0.03 mg) and quaternary naltrexone (1 mg), applied locally in the tail. However, these doses of antagonists injected s.c. in the back did not antagonize local fentanyl. Comparing the relative potency of either agonist or antagonist after local and systemic administration confirmed that the site of action of locally applied mu opioid agonists is in the tail. These results provide evidence that activation of peripheral mu opioid receptors can diminish capsaicin-induced allodynia in primates. This exptl. pain model could be a useful tool for evaluating peripherally acting antinociceptive agents without central side effects and enhance new approaches to the treatment of inflammatory pain.

SO Journal of Pharmacology and Experimental Therapeutics (1998), 286(1), 150-156
CODEN: JPETAB; ISSN: 0022-3565
PY 1998

L4 ANSWER 6 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 6

TI Beneficial effect of the opioid receptor antagonist naltrexone on hypersensitivity induced by spinal cord ischemia in rats: disassociation with MK-801

AU Hao, J. X.; Xu, X. J.; Aldskogius, H.; Seiger, A.; Wiesenfeld-Hallin, Z.

AB In this study, the authors examined the effect of the long-acting opioid antagonist naltrexone on the allodynia-like effect of spinal ischemia in rats. The spinal cord ischemia was induced at midthoracic level by a recently developed photochem. technique using laser irradiation and photoactivatable intravascular dyes. An allodynia

-like sensory disturbance, where the animals reacted by vocalization to non-noxious mech. stimuli in the flank area, was consistently seen during several days after ischemia. Pretreatment with 10 and 20 mg/kg, but not 5 mg/kg naltrexone i.v. 10 min before irradiation decreased the incidence of allodynia. However, even the effect of the highest dose of naltrexone (20 mg/kg) was incomplete, which is in contrast to the effect of the NMDA receptor antagonist MK-801, which has been tested in the same model and found to completely prevent the incidence of allodynia at a dose of 0.5 mg/kg. Pretreatment with sub- or suprathreshold doses of naltrexone (5 and 20 mg/kg resp.) combined with a subthreshold dose of MK-801 (0.1 mg/kg) did not produce a synergistic effect. When naltrexone (20 mg/kg) was administered 10 min after induction of ischemia, it was totally ineffective in decreasing the occurrence and severity of allodynia . In contrast, MK-801 (0.5 mg/kg) still had a good protective effect when injected at this time. Histol. examination showed slight morphol. damage in the spinal cord in 38% of control rats after 1 min laser irradiation without pretreatment with naltrexone. No morphol. abnormalities were observed in rats after pretreatment with naltrexone (20 mg/kg). The results suggest that opioid receptor antagonists and NMDA receptor antagonists prevent a consequence of transient spinal cord ischemia through different mechanisms. High doses of opioid antagonists may have anti-ischemic effects by improving local spinal cord microcirculation and therefore may have a role in preventing ischemia after traumatic spinal cord injury. On the other hand, the NMDA receptor may have a role in the secondary neuronal death resulting from ischemia. Thus, NMDA receptor antagonists may contribute to the prevention of tissue damage by antagonizing the excitotoxic action of glutamate and/or aspartate released by ischemia into the spinal cord. Finally, since only high doses of naltrexone had an effect in the present study, the authors cannot rule out the possibility that this drug may act through non-opioid mechanisms.

SO Restorative Neurology and Neuroscience (1991), 3(5), 257-66
CODEN: RNNEEL; ISSN: 0922-6028
PY 1991

L4 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 7

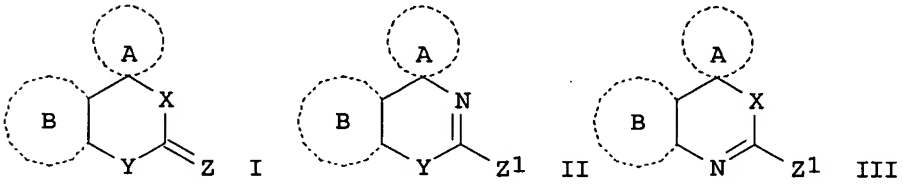
TI Pharmacology of the allodynia in rats evoked by high dose intrathecal morphine

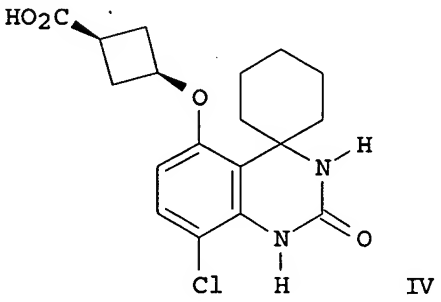
AU Yaksh, T. L.; Harty, G. J.

AB Morphine sulfate in doses of 90 to 150 μg/3 μL evokes a prominent behavioral syndrome characterized by 1) periodic bouts of spontaneous agitation during which the rat scratches and bites at the skin of the caudal dermatomes and 2) vigorous agitation, vocalization and coordinated efforts to bite and escape evoked by a light tactile stimulus applied to the flank, suggestive of a pain state (allodynia). The phenomenon is not reversed by naltexone or is it subject to tolerance. The activities of related opioids and metabolites are discussed. Brief structure-activity relations are given. The observations that the sulfated and conjugated metabolites are 10 to 50 times more potent than their unmetabolized precursor suggest the possibility that, in high concns., certain phenantherene opioid alkaloids with a free 3-OH position, an ether bridge and no N-Me extention will be subject to conjugation and this metabolite will alter the processing of otherwise innocuous tactile stimuli. The coding of light tactile stimulation as non-noxious requires a tonic modulatory influence at the spinal cord level. The fact that morphine at high concns. may exert anti-GABAergic and antiglycinergic effects and the ability of certain spinally administered inhibitory amino acid antagonists to mimic this effect supports this hypothesis.

SO Journal of Pharmacology and Experimental Therapeutics (1988), 244(2), 501-7
CODEN: JPETAB; ISSN: 0022-3565
PY 1988

L4 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
TI Preparation of spiro[cyclohexane-1,4'-quinazoline] derivatives for use as PDE7 inhibitors for the treatment of neuropathic pain
IN Cox, Peter; Kinloch, Ross Anderson; Maw, Graham Nigel
GI




AB Compds. I-III [Ring B = (un)substituted six-membered aryl or heteroaryl ring; Ring A = (un)substituted spirocycle or spiroheterocycle; X = O or NH, NNH2, etc.; Y = O, S, NH, etc.; Z = CHNO2, O, S, etc.; Z1 = H, Me, NH2, etc.] are disclosed as phosphodiesterase 7 (PDE7) inhibitors for use in the manufacture of a medicament for the treatment of neuropathic pain and to a method of treating neuropathic pain using an inhibitor of PDE7. Methods for preparing title compds. are given. Thus, e.g., IV was prepared by substitution of trans-3-[(benzyloxy)methyl]cyclobutyl p-toluenesulfonate (preparation given) with 8'-chloro-5'-hydroxy-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one followed by deprotection and oxidation In PDE7A inhibition assays, IV demonstrated a Ki value of 1.9 (nM).
SO PCT Int. Appl., 108pp.
CODEN: PIXXD2
PY 2006
2006

L4 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
TI Remedy for neuropathic pain
IN Tanabe, Tsutomu
AB It is intended to provide a remedy for neuropathic pain capable of exhibiting an excellent therapeutic effect on neuropathic pain which is an intractable disease. More specifically speaking, a remedy for neuropathic pain which contains an opioid receptor antagonist (in particular, naloxone, naltrexone, naloxonazine, naltrindole, etc.) as the active ingredient; a medicinal composition for treating neuropathic pain which contains an opioid receptor antagonist as the active ingredient; a method of treating neuropathic pain by using an opioid receptor antagonist, and so on.

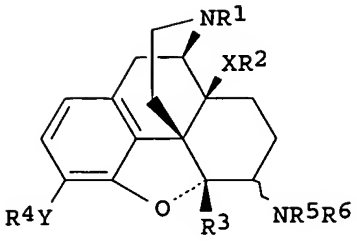
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PY 2006
2006

L4 ANSWER 10 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
TI Method of treating neuropathic pain using a CRTH2 receptor antagonist
IN Corradini, Laura; Field, Mark John; Kinloch, Ross Anderson; Williams-Jones, Bryn Ivor
AB The invention discloses the use of a CRTH2 receptor antagonist in the manufacture of a medicament for the treatment of neuropathic pain and to a method of treating neuropathic pain using an antagonist of CRTH2 receptor.
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
PY 2005
2006
2005
2007

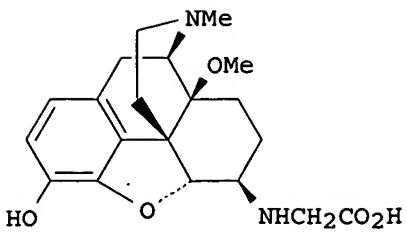
=> d 11-20 ti au abs so py l4

L4 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
TI Methods and materials for the treatment of pain comprising opioid antagonists
IN Burns, Lindsay H.; Schoenhard, Grant L.
AB Methods and compns. for treating subjects with pain, including neuropathic pain, using opioid antagonists are described. Such antagonists are used alone or in combinations with opioid agonists, wherein an opioid antagonist enhances the neuropathic pain-alleviating potency of an opioid agonist. For example, the combination of naltrexone (0.1 ng) and morphine (10 μg), representing a ratio of 1:100,000 of the opioid antagonist to opioid agonist, twice daily, resulted in a significant antihyperalgesic effect in a rat model of neuropathic pain, compared to vehicle or morphine alone for the Day 1 through Day 7 duration. Although morphine alone at 10 μg resulted in 65% and 73% antihyperalgesia on Day 1 and 2, resp., with return to baseline by day 5, the combination of morphine (10 μg) and naltrexone (0.1 ng) resulted in 75, 81, 91, 63, 79, 67 and 56% antihyperalgesia on Days 1 through 7, resp., as well as analgesia (paw withdrawal latencies went above baseline) Days 1 through 7.
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
PY 2004
2005
2004
2004
2005
2006

L4 ANSWER 12 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
TI Method for the production of 6-aminomorphinan derivatives and their use as highly active analgesics
IN Schuetz, Johannes; Schmidhammer, Helmut
GI




I




II

AB The invention relates to the compds., e.g., I [R1 = H, C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C1-6-monohydroxyalkyl, C1-6-dihydroxyalkyl, C1-6-trihydroxyalkyl, C3-10-cycloalkyl-C1-6-alkyl, C3-10-cycloalkyl-C2-6-alkenyl, C3-10-cycloalkyl-C2-6-alkynyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C2-6-alkenyl, C6-10-aryl-C2-6-alkynyl; R2 = R1, C2-6-alkanoyl, C3-6-alkenoyl, C3-6-alkynoyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C3-6-alkenoyl, C6-10-aryl-C3-6-alkynoyl; R3 = H, C1-6-alkyl, C2-6-alkenyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C2-6-alkenyl, C1-6-alkoxy, -C1-6-alkyl, CO2(C1-6-alkyl), CO2H, CH2OH; R4 = C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C3-10-cycloalkyl-C1-6-alkyl, C3-10-cycloalkyl-C2-6-alkenyl, C3-10-cycloalkyl-C2-6-alkynyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C2-6-alkenyl, C6-10-aryl-C2-6-alkynyl, etc.; R5, R6 = H C3-10-cycloalkyl-C1-6-alkyl, C3-10-cycloalkyl-C2-6-alkenyl, C3-10-cycloalkyl-C2-6-alkynyl, C6-10-aryl-C1-6-alkyl, C6-10-aryl-C2-6-alkenyl, C6-10-aryl-C2-6-alkynyl, etc.; X = O, S, CH2; XR2 = H; Y = O; YR4 = H], and their pharmaceutically acceptable acid addition salts, which are useful as highly active analgesics. Thus, aminomorphinan II·1.5 CF3CO2H was prepared from 14-O-methoxymorphone hydrobromide via reductive amination with glycine tert-Bu ester in MeOH containing NaCNBH3 followed by deesterification with CF3CO2H in CH2Cl2. Aminomorphinan II·1.5 CF3CO2H was tested for analgesic activity [Ki = 0.83 nM for opioid receptor; ED50 = 28 μg/kg s.c. and ED50 = 0.42 μg/kg i.cv. in rat tail flick test; ED50 = 500 μg/kg s.c. and ED50 = 0.42 μg/kg i.cv. respiratory depression in rats; ED50 = 100 μg/kg s.c. antiallodynic effect in rats].

SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
PY 2003
2003
2003
2003
2004
2006
2004
2005
2005
2005
2006
2006
2005
2006
2004
2005

L4 ANSWER 13 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

TI Effects of Korean red ginseng extract on neuropathic pain induced by chronically constrictive ligatures of the sciatic nerve in the rat

AU Kim, Young-In; Kim, Kwang-Jin

AB Mech. injuries of peripheral nerves disturb the reciprocal fast and slow communication between periphery and central nervous system and may lead to

variety of clin. pain syndromes, including the hyperalgesia, allodynia, and spontaneous pain. One of the effective animal models used for this study is the "chronic constriction injury (CCI)" method, described by Bennett and Xie. The extract of Korean red ginseng (Panax ginseng C.A. Meyer) has been known to produce a variety of effects mediated by central nervous system. Especially, it showed inhibitory effect on morphine tolerance and dependence, and decreased the serotonin release from the brain stem. Recent studies suggested that the extract clearly showed analgesic and hypothermic effects in the rat at relatively high doses, and these effects were not mediated via endogenous opiates or opiate receptors since the effects were not antagonized by naltrexone. This study was undertaken to determine the effects and their mechanisms of a standard Korean red ginseng extract on peripheral neuropathic pain induced by the CCI method. The hind paw withdrawal responses as a indicator of pain were determined by the mech. (von Frei filaments: 0.8 gm and 4.2 gm), thermal (5°C, 30°C and 44°C) and acetone stimuli to compare with both effects before and after the i.p. injection of ginseng extract (200 mg/kg). Morphine (5 mg/kg, i.m.), ketamine (3 mg/kg, i.m.), and guanethidine (30 mg/kg, i.p.) were administered after injection of ginseng extract The results of the present study were summarized as follows:. 1. Ginseng extract did not show a significant analgesic effect in mech. allodynia and thermal hyperalgesia and allodynia. 2. Ginseng extract increased the hind paw sensitivity to some stimuli. 3. Ginseng extract produced significant inhibitory effect on the hind paw withdrawal responses to acetone stimuli. 4. Morphine showed inhibitory effect on the responses to noxious cold, acetone, and heat stimuli. The effects of morphine, however, were antagonized significantly by the ginseng extract 5. Ketamine, non-competitive antagonist of N-methyl-D-aspartate, showed significant inhibitory effect to noxious cold and acetone stimuli. 6. Guanethidine, chemical sympathetic blocker, showed no significant effects on the responses to noxious cold and heat stimuli, and acetone stimuli. These results suggested that the ginseng extract showed partially analgesic effect in disorders of pain sensation, and the hyperesthesia produced in this animal pain model was not dependent on the chemical sympathectomy. This effect might be a result from the depression of both the dorsal horn neurons in the spinal cord and the nociceptors sensitized by continuous impulse discharges at the nerve injury sites, and may be produced via a non-opioid mechanism.

SO Chungnam Uidae Chapchi (1995), 22(2), 209-223
CODEN: CUCHDS; ISSN: 0253-6307
PY 1995

L4 ANSWER 14 OF 33 MEDLINE on STN

TI Reversal of ongoing thermal hyperalgesia in mice by a recombinant herpesvirus that encodes human preproenkephalin.

AU Yeomans David C; Jones Toni; Laurito Charles E; Lu Ying; Wilson Steven P

AB Herpesvirus-mediated transfer of the human preproenkephalin gene to primary afferent nociceptors prevents phasic thermal allodynia /hyperalgesia in mice. It is not known, however, whether similar viral treatments would reverse ongoing or chronic pain and allodynia /hyperalgesia. To this end, mice were given intrathecal injections of pertussis toxin (PTX), which produces a weeks-long thermal hyperalgesia apparently by uncoupling certain G proteins from inhibitory neurotransmitter receptors. This treatment produced profound thermal hyperalgesia in both Adelta and C-fiber thermonociceptive tests lasting at least 6 weeks. However, treatment of skin surfaces with an enkephalin-encoding herpesvirus, but not control virus or vehicle, completely reversed this hyperalgesia. This profound anti-hyperalgesia was observed for both Adelta- and C-fiber-mediated responses. Interestingly, however, while the anti-hyperalgesic effect of the enkephalin-encoding virus on C-fiber-mediated responses was reversed by intrathecal application of micro or delta opioid antagonists, only delta antagonists reversed the effect of this virus on Adelta hyperalgesia.

Thus, virus-mediated delivery of the proenkephalin cDNA reverses thermal hyperalgesia produced by PTX-induced ribosylation of inhibitory G proteins by an opioid-mediated mechanism. These results suggest that herpesvirus vectors encoding analgesic peptides may be useful in attenuating centrally mediated, ongoing neuropathic pain and/or hyperalgesia.

SO Molecular therapy : the journal of the American Society of Gene Therapy, (2004 Jan) Vol. 9, No. 1, pp. 24-9.
Journal code: 100890581. ISSN: 1525-0016.

PY 2004

L4 ANSWER 15 OF 33 MEDLINE on STN

TI Enhancement of the effects of a complete inhibitor of enkephalin-catabolizing enzymes, RB 101, by a cholecystokinin-B receptor antagonist in diabetic rats.

AU Coudore-Civiale M A; Meen M; Fournie-Zaluski M C; Boucher M; Roques B P; Eschalier A

AB 1. RB 101, a complete inhibitor of enkephalin-catabolizing enzymes, has been previously shown to produce antinociception in normal rats after systemic administration. Moreover, its coadministration with a cholecystokinin-B (CCK-B) receptor antagonist has been shown to strongly enhance its antinociceptive effect in normal rats. In this work, we determined whether RB 101 was able to reduce hyperalgesia and allodynia in diabetic rats, a model of neuropathic pain. The type of opioid receptors (mu or delta) involved was determined using naloxone and naltrindole, respectively, and the interactions between endogenous enkephalins and CCK on nociception control was investigated using coadministration of RB 101 and the CCK-B receptor antagonist CI-988. 2. RB 101 suppressed mechanical hyperalgesia (paw pressure-induced vocalization test), partially alleviated mechanical allodynia (von Frey hair test), and was ineffective in thermal allodynia (tail immersion test). The analgesic effect was completely cancelled by naloxone or naltrindole, suggesting that is requires the availability of mu- and/or delta-opioid receptors. 3. The combination of an inactive dose of CI-988 with the lowest effective dose of RB 101 resulted in a stronger increase in the vocalization threshold comparatively to RB 101 alone. 4. The present study demonstrates that the antinociception generated by RB 101 induced by elevation of extracellular levels of endogenous enkephalins, can be extended to neuropathic pain in diabetic rats and that blockade of CCK-B receptors potentiated antinociceptive effects elicited by RB 101.

SO British journal of pharmacology, (2001 May) Vol. 133, No. 1, pp. 179-85.
Journal code: 7502536. ISSN: 0007-1188.

PY 2001

L4 ANSWER 16 OF 33 MEDLINE on STN

TI The role of delta-opioid receptor subtypes in neuropathic pain.

AU Mika J; Przewlocki R; Przewlocka B

AB A large body of evidence suggests an important role of delta-opioid receptor agonists in antinociception at the level of the spinal cord. Our study was undertaken to analyse the spinal antinociceptive and antiallodynic effects of delta(1)- and delta(2)-opioid receptor agonists and antagonist after their acute and chronic intrathecal administration in a neuropathic pain model in the rat. In rats with a crushed sciatic nerve, the delta(1)-opioid receptor agonist [D-Pen(2), D-Pen(5)]enkephalin (DPDPE, 5-25 microg i.t.) and the delta(2)-opioid receptor agonist deltorphin II (1.5-25 microg i.t.) dose dependently antagonized the cold-water allodynia which developed after sciatic nerve injury. These effects of DPDPE were antagonized by 7-benzylidenenaltrexon (BNTX, 1 microg i.t.) while the effects of deltorphin II were antagonized by 5'naltrindole izotiocyanate (5'NTII, 25 microg i.t.). Both agonists had a dose-dependent, statistically significant effect on the tail-flick latency in two tests, with focused light and cold water. Chronic administration of DPDPE (25 microg i.t.) and deltorphin II (15 microg i.t.) resulted in significant prolongation of the reaction time determined on days 2, 4 and

6 post-injury. In conclusion, our results show an antiallodynic and antinociceptive action of DPDPE and deltorphin II at the spinal cord level, which suggests that both delta-opioid receptor subtypes play a similar role in neuropathic pain. This indicates that not only delta(1)- but also delta(2)-opioid receptor agonists can be regarded as potential drugs for the therapy of neuropathic pain.

SO European journal of pharmacology, (2001 Mar 9) Vol. 415, No. 1, pp. 31-7. Journal code: 1254354. ISSN: 0014-2999.

PY 2001

L4 ANSWER 17 OF 33 MEDLINE on STN

TI Activation of peripheral kappa opioid receptors inhibits capsaicin-induced thermal nociception in rhesus monkeys.

AU Ko M C; Butelman E R; Woods J H

AB 8-Methyl-N-vanillyl-6-nonenamide (capsaicin) was locally applied in the tail of rhesus monkeys to evoke a nociceptive response, thermal allodynia, which was manifested as reduced tail-withdrawal latencies in normally innocuous 46 degrees C water. Coadministration of three kappa opioid ligands, U50,488 (3.2-100 microgram), bremazocine (0.1-3.2 microgram), and dynorphin A(1-13) (3.2-100 microgram), with capsaicin in the tail dose-dependently inhibited capsaicin-induced allodynia. This local antinociception was antagonized by a small dose of an opioid antagonist, quadazocine; (0.32 mg), applied in the tail; however, this dose of quadazocine injected s.c. in the back did not antagonize local U50,488. Comparing the relative potency of either agonist or antagonist after local and systemic administration confirmed that the site of action of locally applied kappa opioid agonists is in the tail. In addition, local nor-binaltorphimine (0.32 mg) and oxilorphan (0.1-10 microgram) antagonist studies raised the possibility of kappa opioid receptor subtypes in the periphery, which indicated that U50,488 produced local antinociception by acting on kappa1 receptors, but bremazocine acted probably on non-kappa1 receptors. These results provide functional evidence that activation of peripheral kappa opioid receptors can diminish capsaicin-induced allodynia in primates. This experimental pain model is a useful tool for evaluating peripherally antinociceptive actions of kappa agonists without central side effects and suggests new approaches for opioid pain management.

SO The Journal of pharmacology and experimental therapeutics, (1999 Apr) Vol. 289, No. 1, pp. 378-85. Journal code: 0376362. ISSN: 0022-3565.

PY 1999

L4 ANSWER 18 OF 33 MEDLINE on STN

TI Dynorphin A increases substance P release from trigeminal primary afferent C-fibers.

AU Arcaya J L; Cano G; Gomez G; Maixner W; Suarez-Roca H

AB Dynorphin A-(1-17) has been found to produce spinal antianalgesia and allodynia. Thus, we studied whether dynorphin A-(1-17) modulates substance P release evoked by the C-fiber-selective stimulant capsaicin (1 microM) from trigeminal nucleus caudalis slices. Very low concentrations of dynorphin A-(1-17) (0.01-0.1 nM) strongly facilitated capsaicin-evoked substance P release. This dynorphin A-(1-17) effect was not blocked by the opioid receptor antagonists naloxone (100 nM), beta-funaltrexamine (20 nM), naloxonazine (1 nM), nor-binaltorphimine (3 nM) and ICI 174,864 (N,N-dialyl-Tyr-Aib-Phe-Leu; 0.3 microM). Yet, the effect of dynorphin A-(1-17) was blocked by the NMDA receptor antagonist MK-801 ((+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-10-imine maleate; 0.3 microM). Neonatal treatment with capsaicin (50 mg/kg s.c.), which destroys substance P-containing primary afferents, abolished the excitatory effect of dynorphin A-(1-17) on K+-evoked substance P release. In conclusion, dynorphin A-(1-17) increases substance P release from C-fibers by the activation of NMDA receptors which supports the involvement of presynaptic mechanisms in dynorphin-induced antianalgesia and allodynia.

SO European journal of pharmacology, (1999 Jan 29) Vol. 366, No. 1, pp. 27-34.
Journal code: 1254354. ISSN: 0014-2999.
PY 1999

L4 ANSWER 19 OF 33 MEDLINE on STN
TI Evidence that spinal endogenous opioidergic systems control the expression of chronic pain-related behaviors in spinally injured rats.
AU Hao J X; Yu W; Xu X J
AB We have previously reported that ischemic spinal cord injury in rats leads to chronic pain-related behaviors. Thus, rats exhibited aversive reactions to innocuous mechanical stimuli (mechanical allodynia) applied to a body area at or rostral to the dermatomes innervated by the injured spinal segments. The responses of the rats to cold are also markedly enhanced (cold allodynia). Interestingly, more than 50% of spinally injured rats did not develop these abnormal pain-related behaviors after spinal cord injury. In the present study, we showed that the extent of injury is similar between allodynic and non-allodynic rats. Furthermore, intrathecal (i.t.) naloxone, a broad-spectrum opioid receptor antagonist, reversibly provoked mechanical and cold allodynia-like responses in spinally injured rats that did not develop such behaviors spontaneously. However, naloxone did not elicit such reactions in normal rats and did not alter the tail-flick latency in normal or spinally injured rats. Furthermore, i.t. D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH2 (CTOP) or naltridole, selective antagonists of mu and delta opioid receptors, respectively, also triggered pain-related behaviors similarly to naloxone. Although norbinaltorphimine (nor-BIN), a selective kappa-receptor antagonist, also elicited such responses, the time course of the effect makes it unlikely that spinal kappa-receptors were involved. These results suggested that the expression of abnormal pain-related behaviors in some spinally injured rats is tonically suppressed by the spinal opioidergic system. Interindividual differences that lead to lack or dysfunction of such inhibition may underly the appearence of pain-related behavior in some, but not all, spinally injured rats. It is suggested that such inhibition is exerted through spinal mu and delta, but not kappa, opioid receptors. The endogenous opioidergic control appears to be only active against abnormal painrelated behaviors in spinally injured rats. Our results are relevant for the clinical observation that only a subgroup of patients with nerve injury suffers from neuropathic pain.
SO Experimental brain research. Experimentelle Hirnforschung. Experimentation cerebrale, (1998 Jan) Vol. 118, No. 2, pp. 259-68.
Journal code: 0043312. ISSN: 0014-4819.
PY 1998

L4 ANSWER 20 OF 33 MEDLINE on STN
TI Antiallodynic effects of a CCKB antagonist in rats with nerve ligation injury: role of endogenous enkephalins.
AU Nichols M L; Bian D; Ossipov M H; Malan T P Jr; Porreca F
AB Cholecystokinin (CCK) may act as an endogenous anti-opioid and blockade of CCK receptors can enhance the potency and efficacy of morphine. This effect is blocked by opioid delta (delta) receptor antagonists, suggesting a tonic inhibitory action of CCK to diminish the release and/or availability of endogenous enkephalins. The present studies have further evaluated this possibility by studying the antiallodynic actions of a CCKB antagonist (L365,260) alone, or in the presence of thiorphan (a neutral endopeptidase inhibitor) in a model of peripheral neuropathy. Animals subjected to nerve injury, but not sham controls, exhibited long lasting, stable mechanical allodynia. Intrathecal (i.t.) administration of L365,260 or thiorphan alone did not alter allodynia. However, co-administration of these compounds produced a significant antiallodynic action which was antagonized by receptor selective doses of naltrindole, an opioid delta receptor antagonist. In addition, antisera to [Leu5]enkephalin, but not to [Met5]enkephalin, also blocked the

antiallodynic action of thiorphan plus L365,260. These data suggest that blockade of CCKB receptors may enhance the actions or availability of endogenous [Leu5]enkephalin or a like substance which can elicit a significant antiallodynic action via opioid delta receptors when its degradation is by inhibited by thiorphan. The data suggest that delta opioids are involved in regulation of some aspects of nerve-injury induced pain.

SO Neuroscience letters, (1996 Sep 13) Vol. 215, No. 3, pp. 161-4.
Journal code: 7600130. ISSN: 0304-3940.
PY 1996

=>